IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION UNDER 37 C.F.R. 1.132	Attorney Docket No.	CALD-005
	First Named Inventor	CALDWELL, LARRY
	Confirmation Number	3760
	Application Number	10/029,408
	Filing Date	December 26, 2001
	Group Art Unit	1618
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Jake Minh Vu
	Title: Methods and Compositions for Treating Carpal Tunnel Syndrome	

Dear Sir:

I, Larry Caldwell, am an inventor of the subject matter claimed in the patent application identified above. A copy of my C.V. which demonstrates that I am qualified to speak on the level of one of ordinary skill in the art is already of record.

I hereby declare as follows:

1. I have read the Office Action dated May 27, 2010 that issued in the above referenced application. I understand that the Examiner has rejected the pending claims on the basis that they are allegedly obvious in view of the combined teaching of Bockow (U.S. Patent No. 5,709,855), Edwards (U.S. Patent No. 5,989,559), Herbert *et al.* (American J. of Industrial Medicine 37: 62-74, 2000), Hirano *et al.* (U.S. Patent No. 5,869,087), Liebschutz *et al.* (WO 02/22109) and the Applicants' specification.

2. For the reasons set forth below, this Declaration demonstrates that:

a) the cited references fail to teach or suggest the amelioration of at least

one symptom associated with median nerve pressure for a period of 1 week or longer; and

b) one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the claimed method based on Edwards' examples.

3. The combined teaching of the cited references fails to teach or suggest the amelioration of at least one symptom associated with median nerve pressure for a period of 1 week or longer

I understand that the basis for the rejection of the claims by the Office is Example P of Edwards. This example describes application of a banana peel extract formulation to the wrist of a subject. In Example P, Edwards describes that the subject experienced less swelling and pain in her arm after application of the extract cream. However, nowhere in Example P does Edwards teach that the symptoms of the subject were ameliorated for an extended period of time, i.e., 1 week or longer. Just because Edwards' extract cream may give immediate relief of symptoms does not mean that the cream would work over an extended period of time, i.e., a period of 1 week or longer.

As such, Edwards' Example P does not teach or suggest amelioration of at least one symptom associated with median nerve pressure for a period of 1 week or longer, as claimed. Accordingly, the combined teaching of the cited references fails to teach or suggest the above claim element.

4. Edwards' Example P does not support a reasonable expectation of success in practicing the claimed method

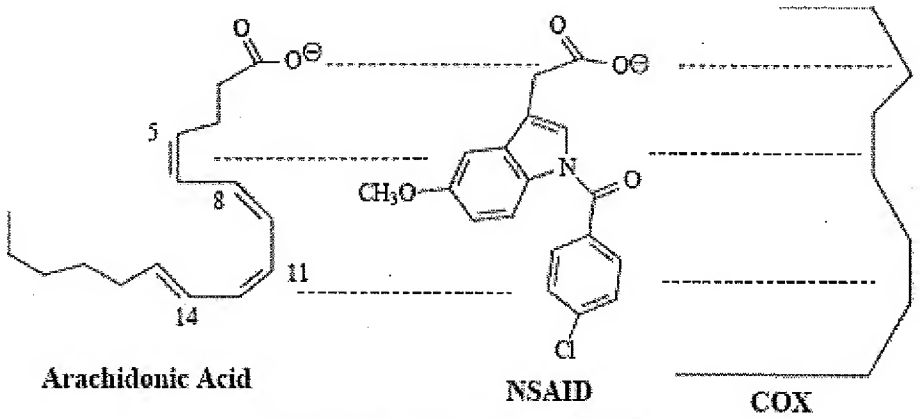
I understand that the Office relies on Example P of Edwards for allegedly providing a working exemplification that supports an reasonable expectation of success in practicing the claimed method. However, Edwards' banana peel extract does not support a reasonable expectation of success because Edwards' active agents have

completely different structures and mechanisms of action compared to NSAIDs and Edwards' results would not be extrapolated to a NSAID formulation, as is demonstrated below.

(a) *Edwards' active agents lack essential structural feature of NSAIDs*

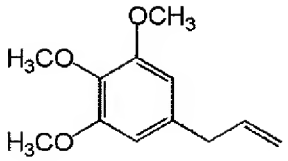
Edwards teaches that the likely active agents of the banana peel extract are the compounds elemicin and homosalate (see Table 3, Edwards). However, elemicin and homosalate have distinct structures compared to an NSAID because they lack an essential structural feature, as shown below.

As demonstrated in Exhibit A (see page 4), NSAIDs all include an acidic group that is essential for their mechanism of action, i.e., inhibition of the enzyme COX. This acidic group mimics the acidic group of the native enzyme substrate arachidonic acid, as depicted below (Exhibit A, page 2). See also, the present specification, page 5, lines 8-11.

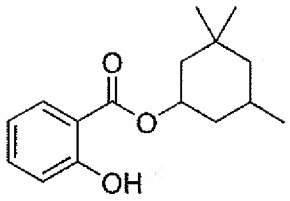


Inhibition of COX by NSAIDs

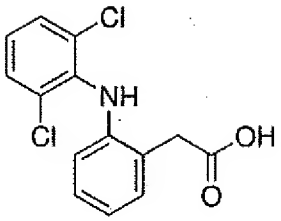
Edwards' elemicin and homosalate lack the structural feature of an acidic group that is important to the activity of an NSAID drug, e.g., diclofenac, (see specification, page 5, lines 8-11, and structures illustrated below) and thus could not act via the same mechanism of action.



Elemicin



Homosalate



Diclofenac

(b) *Edwards' active agents act by completely different mechanisms of action*

Not only do Edwards' elemicin and homosalate have different structures than NSAIDs, but these compounds also have completely different mechanisms of biological action compared to an NSAID. Elemicin is found in nutmeg and is a known neuromodulator (Exhibit B) that is partly responsible for the anticholinergic-like effects of raw nutmeg (Exhibit C). As such, elemicin's mechanism of action is via blocking the neurotransmitter acetylcholine in the central and peripheral nervous system. For example, acetylcholine acts in the peripheral nervous system to activate muscles.

Homosalate is a common ingredient of lotions such as moisturizers and sunscreens because of its UV blocking properties (see Edwards, Example F), and is reported to have activity in vitro as an anti-androgen and estrogen, i.e., as a mimic of the steroid hormones androgen and estrogen (see Exhibit D, abstract, where homosalate (HMS) activity is described). As such, homosalate's mechanism of action is as a **steroid** receptor antagonist.

In contrast, **non-steroidal** NSAIDs are a class of non-narcotic drugs that are distinct from the **steroid** opiod drugs which are additive. NSAIDs' mechanism of action is to inhibit prostaglandin synthesis via inhibition of cyclooxygenase (COX) and thus the activity of prostaglandins as messenger molecules in inflammation processes (Exhibit A). It is well understood in the art that **non-steroidal** NSAIDs' mechanism of action is clearly distinct from that of **steroid** anti-inflammatory drugs (see e.g., Exhibit E, page 1 where narcotic opioid drugs are contrasted with NSAIDs).

However, Edwards' active agents have very different properties. Elemicin has a completely different mechanism of action compared to an NSAID because it acts in the nervous system via blocking neurotransmitters rather than acting locally via inhibition of inflammation signaling pathways. Finally, homosalate acts by mimicking the action of a steroid at a steroid receptor, and as such is clearly different from a **non-steroidal** NSAID.

As such, the active agents of the banana peel extract have distinct structures and completely different mechanisms of action compared to the NSAIDs of the claimed invention.

Thus, those skilled in the art would not extrapolate any results obtained with Edwards' extract to an NSAID transdermal formulation.

5. No reduction to practice prior to the working exemplification of subject application

I am aware of no report of using a topical NSAID formulation to treat symptoms of carpal tunnel syndrome/median nerve pressure prior to the priority date of the current application. The present specification provides actual working exemplification of a diclofenac transdermal patch that ameliorated all symptoms of tingling, numbness and pain associated with carpal tunnel syndrome in a subject for a period of three weeks.

Prior to the actual reduction to practice reported in the subject application, it was not at all certain that application of a NSAID topical formulation would result in amelioration of at least one symptom associated with carpal tunnel syndrome/median nerve pressure, much less amelioration for a period of 1 week or longer.

6. No reasonable expectation of success in practicing the claimed method

As such, prior to the work described in the subject application, one of ordinary skill in the art could not have had a reasonable expectation of success in a method of topically applying an NSAID formulation to ameliorate at least one symptom of carpal tunnel syndrome/median nerve pressure for a period of one week or longer. This lack of reasonable expectation of success in the claimed methods is based on the following premises:

(a) As discussed above, based on Edwards' Example P, one of ordinary skill in the art would not know whether a topical NSAID formulation could be applied to result in amelioration of symptoms of carpal tunnel syndrome/median nerve pressure. Edwards' active agents, elemicin and homosalate, lack an essential structural feature of an NSAID and could not act via the same mechanism of action. Further, Edwards' active agents have completely different mechanisms of action compared to an NSAID. Thus those skilled in the art would not extrapolate any results obtained with Edwards' extract to an NSAID transdermal formulation; and

(b) It is well-known in the art that just because one topical formulation is administered to treat a condition does not mean that a different topical formulation containing a different active agent can also be effective in treating that condition. This is particularly true if the active agents have different mechanisms of action.

Accordingly, in view of the above, based on the cited prior art teachings but without actual reduction to practice evidence, one of skill in the art would not have had a reasonable expectation of success in practicing the claimed methods of topically applying an NSAID formulation to ameliorate at least one symptom associated with pressure applied to the median nerve of the carpal tunnel of a host for a period of 1 week or longer.

7. I hereby declare that all statements made herein are of my own knowledge and are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issued there from.

Respectfully submitted,

Date: 10/27/10 By: Larry J Caldwell

Larry Caldwell

Enclosed:

Exhibit A: Jack DeRuiter, "Non-steroidal anti-inflammatory drugs (NSAIDS)," Principles of Drug Action 2, Fall 2002, www.duc.auburn.edu/~deruija/nsaids_2002.pdf

Exhibit B: Sangalli et al., "Toxicology of Nutmeg Abuse," Clinical Toxicology, 2000, Vol. 38, No. 6, pages 671-678

Exhibit C: McKenna A, Nordt SP, Ryan J (August 2004). "Acute nutmeg poisoning". European Journal of Emergency Medicine : Official Journal of the European Society for Emergency Medicine 11 (4): 240–1

Exhibit D: Ma et al., "UV Filters with Antagonistic Action at Androgen Receptors in the MDA-kb2 Cell Transcriptional-Activation Assay," Toxicol. Sci. (2003) 74 (1): 43-50

Exhibit E: Nuutinen and Raj, "An overview of current and investigational non-narcotic drugs for treatment of acute and chronic pain" Current Pain and Headache Reports, Volume 2, Number 3, 187-192, 1998